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# EXPERIMENTAL "RHEUMATIC MYOCARDITIS."*

## EXPERIMENTAL STREPTOCOCCAL FOCAL LESIONS IN THE HEART MUSCLE OF RABBITS SIMILAR TO LESIONS IN THE HUMAN HEART IN RHEUMATISM.

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Good accounts of the structure of the nodular lesions in the heart muscle in rheumatic myocarditis are found in the articles by Aschoff,[1] Geipel,[2] Coombs,[3] Gallavardin,[4] and others. In most of the accounts of these alterations credit is given to Romberg[5] for first reporting their occurrence. Since the nodules are on the border-line of visibility, they doubtless have been seen by many observers, and careful search of the literature might disclose that others besides Romberg have described such changes and like Romberg failed to attach much significance to them.

One such observation about the same time as Romberg's is that by Bret.[6] In describing the changes in the heart muscle of a girl of seventeen who died from acute rheumatism with pericarditis, he mentions discrete localized changes deep in the muscle unconnected with the pericarditis, made up of embryonal cells and located about the septa.[7]

By a number of writers the foci are referred to as the "Aschoff-Geipel nodules." Certainly the credit for suggesting the specific

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[1] *Verhandl. deut. path. Gesellsch.*, 1904, 8, p. 46; Aschoff and Tawara, *Die heutige Lehre von den pathologisch-anatomischen Grundlagen der Herzschwäche*, Jena, 1906; *Brit. Med. Jour.*, 1906, 2, p. 1103.

[2] *Deutsche Arch. f. klin Med.*, 1905, 85, p. 75; *München. med. Wchnschr.*, 1909, 56, p. 2469.

[3] *Brit. Med. Jour.*, 1907, 2, p. 1513; *St. Mary's Hosp. Gaz.*, 1910, 16, p. 121; *Jour. Path. and Bact.*, 1910–11, 15, p. 489.

[4] *Lyon med.*, 1908, 110, p. 753, and 1911, 117, p. 149.

[5] *Deut. Arch. f. klin. Med.*, 1894, 53, p. 141.

[6] *La Province Méd.*, 1894, 8, p. 437.

[7] The more significant of his observations of the changes are stated as follows: "Indépendament de ces foyers de prolifération embryonnaire périvasculaire, il existe, dans la profondeur du muscle cardiaque, à une distance notable du péricarde inflammé, d'autres foyers que paraissent absolument indépendants de toute connexion vasculaire ou conjonctive. Ce sont pour la plupart des amas arrondis ou des traînées culaires, dans l'intervalle de ces derniers. Ils offrent une constitution uniforme qui est à peu près la suivante: la partie centrale de ces foyers inflammatoires est formée de blocs opaques caséifiés, fixant très fortement la couleur; ils semblent résulter, selon nous, de la dégénérescence des fibres musculaires cardiaques. A leur pourtour se dispose une multitude d' éléments embryonnaires."

relationship of the nodules to the infectious agent of acute articular rheumatism may be properly given to Aschoff and Geipel. In 1909 Geipel states that the total number of cases in which nodules had been found, and associated with rheumatism by the writers, was 24. He fails to include in this enumeration the four cases of Saigo referred to by him in his first article.

Geipel, and following him a number of writers, have found it difficult to account for their presence in the heart muscle of a boy of eleven who died of chronic nephritis, obliteration of the pericardium, and verrucose mitral endocarditis, on account of the absence of joint involvement clinically. With this exception, the legitimacy of which as an exception may very well be questioned, there are but few comments in the literature pertaining to these lesions in the human myocardium opposing their specific limitation to rheumatism.

The most recent advocate of their etiology in the rheumatic infection is Fraenkel,[1] who found them in 17 of 20 cases with a history of rheumatism. He concludes that although not present perhaps in the hearts of all who have had acute articular rheumatism, their presence indicates that infection with the agent of this disease has at some time taken place.

In the course of examinations of animal reactions to streptococci, to which reference has been made by D. J. Davis,[2] opportunity has been afforded to examine the heart muscle of rabbits injected with various strains of streptococci. All of the streptococci were of the type described by Davis and Rosenow[3] in the recent milk epidemic of sore throat in Chicago, with exception of two, a streptococcus viridans and a hemolytic streptococcus.

*Changes in a rabbit killed two hours after a single intravenous injection of the 24-hour growth at 37° C. on two blood agar slants of a streptococcus (236) isolated by Dr. Davis from the serofibrinous peritoneal exudate found at necropsy, and producing arthritis in rabbits. The peritonitis was a sequence of sore throat during the milk epidemic.*[4]—Sections of the heart muscle contain small groups of cells quite uniformly distributed. Any low-power field of these sections contains from three to six or eight of these lesions. They occupy the space between one or more muscle fibers with their long axis parallel with the fibers, and contain from 10 or 15 to 100 cells. The most conspicuous and usually the larger number of cells are large with large oval or round, sometimes irregular, nuclei which stain unevenly and rather lightly and may be centrally or a little eccentrically placed. The cytoplasm stains faintly and forms a rim about the nucleus about one-third the diameter of the nucleus. The size of the cells varies considerably and it is not difficult to find cells of this type containing two, sometimes six or eight streptococci. In addition to these large cells and almost as numerous, are smaller cells with more deeply stained nuclei and a small amount of cytoplasm. They are irregularly disseminated as are also a few polymorphonuclear leukocytes.

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[1] *Beitr. sur path. Anat. u. z. allg. Path.*, 1912, 52, p. 597.

[2] *Jour. Am. Med. Assoc.*, 1912, 58, p. 1283.

[3] *Ibid.*, p. 773.

[4] J. A. Capps and J. L. Miller, *ibid.*, p. 1848.

*Changes in a rabbit killed 10 hours after a single intravenous injection with the same streptococcus (236) using the growth from four blood agar slants after 24 hours at 37° C.*—There are large collections of bacteria in the minute blood vessels. No necrosis is observed about these collections nor is there any cellular infiltration about them.

*Changes in a rabbit killed 24 hours after a single injection of the growth on two blood agar slants of the same streptococcus (236).*—The lesions which are most conspicuous and numerous are about 0.25 mm. in diameter, rounded or oblong in shape according to the direction of the section in relation to the muscle fibers. They contain solid masses of bacteria separating or replacing necrotic muscle fibers. There is a tendency in some of the lesions for the masses of bacteria to appear at the periphery, leaving the center fairly clear or containing scattered chains of cocci and necrotic muscle fibers, in others the bacteria are more evenly distributed, and in still others the bacterial masses are very definitely outlined as though occupying the lumen of a vessel. There is no infiltration of cells in the vicinity of these regions and the muscle fibers immediately surrounding them are necrotic. Other minute focal lesions consisting of collections of mononuclear cells occur but are not numerous, one or two being found in some sections, in others, none. The cells in these lesions are large, lightly stained, irregularly shaped, with large round or oval nuclei, and smaller cells with more deeply stained nuclei. The two varieties occur in about equal numbers. Some of the large cells contain bacteria. A few scattered chains of cocci are sometimes present in the periphery of the lesions.

*Changes in a rabbit dying spontaneously two days after a single intravenous injection of the 24-hour growth on one blood agar slant of a streptococcus (214) isolated by Dr. Davis from suppurating lymph glands secondary to a sore throat.*—There are many necrotic regions containing bacteria. These lesions are round, oval, or spindle shaped according to the direction of the section, and some of the largest lesions are 1.5–0.6 mm. in diameter. The organisms are frequently arranged in clumps, distributed rather uniformly through the central portion, in others they form a ring near the periphery, and in a few, one large, dense mass. Necrosis is a marked feature of these lesions, and muscle fibers in the center of some stain faintly and have partially disappeared. The necrosis often extends for a considerable distance beyond that portion of the lesion occupied by bacteria and may equal the width of two or three fibers. On the other hand, a few lesions possess but very slight necrosis about the bacteria and there is a general infiltration with polymorphonuclear cells. There is considerable nuclear fragmentation in these cells, and about the borders of these regions there are many eosinophiles. A slight modification of the alterations described consists of small collections of large and small mononuclear cells about blood vessels in about equal numbers, together with some polymorphonuclear leukocytes and eosinophiles. Bacteria are found in some of the large mononuclear cells in these lesions but they do not occur in clumps.

*Changes in two rabbits dying spontaneously three days after single intravenous injections of the 24-hour growth on blood agar slants of* (1) *a streptococcus* (*219*) *isolated by Dr. Davis from the pus obtained during life from a brain abscess following sore throat, and* (2) *streptococcus* (*233*) *obtained from the spinal fluid during life in a case of meningitis following sore throat.*—Sections from the heart muscle of these rabbits present lesions which are in many respects similar, and, with a few exceptions, one description will answer for both. The lesions containing bacteria without any cellular infiltration average about 3–5 cm. in section, 1–0.5 cm. in diameter. They are larger and associated with more necrosis in the muscle of Rabbit 1. In a few the bacteria are arranged in dense rounded masses but in one heart muscle they occupy the intermuscular spaces and tend to form a meshwork or one or more long narrow bands sometimes definitely outlined as though filling the lumen of a vessel. Others are frequently located near blood vessels and arranged as a wall on one or both sides of the blood vessels. In addition to such changes there are also small collections (Fig. 1) of mononuclear cells and in about the same frequency as the patches of necrosis with bacteria. These collections of cells vary considerably in size, some containing 15–20, others, 100 or more cells. By far the majority are large mononuclear cells, small mononuclears comprising about one-third. Polymorphonuclear leukocytes are very rare.

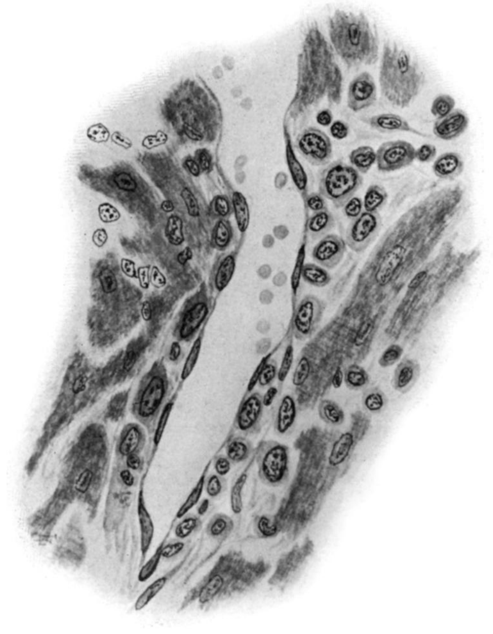

FIG. 1.—Perivascular collection of large mononuclear cells in the heart of a rabbit dying three days after inoculation of streptococcus (219) from a brain abscess following sore throat.

In a third variety of focal inflammation, bacteria are distributed throughout and there is a general infiltration with polymorphonuclear leukocytes and mononuclear cells with a considerable amount of nuclear fragmentation.

In some of the sections of a series there were typical abscesses with central masses of bacteria radially arranged at the margin with zones of polymorphonuclear leukocytes about them; still more externally, narrow zones of necrotic muscle fibers, the whole surrounded by muscle fibers pushed to either side. In tissue surrounding these abscesses polymorphonuclear leukocytes are quite abundant but scatteringly arranged.

*Changes in a rabbit dying spontaneously five days after a single intravenous injection of the 24-hour growth on a single blood agar slant of a streptococcus* (*35*) *sent to Dr. Davis* *by Dr. Fabyan of Boston, and isolated from erysipelas complicating sore throat in the Boston milk epidemic.*—There are small lesions (17 in sections 2–0.3 cm. in diameter), most of them near the outer surface of the heart. In many of them bacteria are found filling the lumen of vessels. In some only bacteria are present, in others there is a rather uniform admixture of disintegrating cells. In places about these lesions are collections of large endothelial cells with a few polymorphonuclear leukocytes, containing considerable nuclear fragmentation.

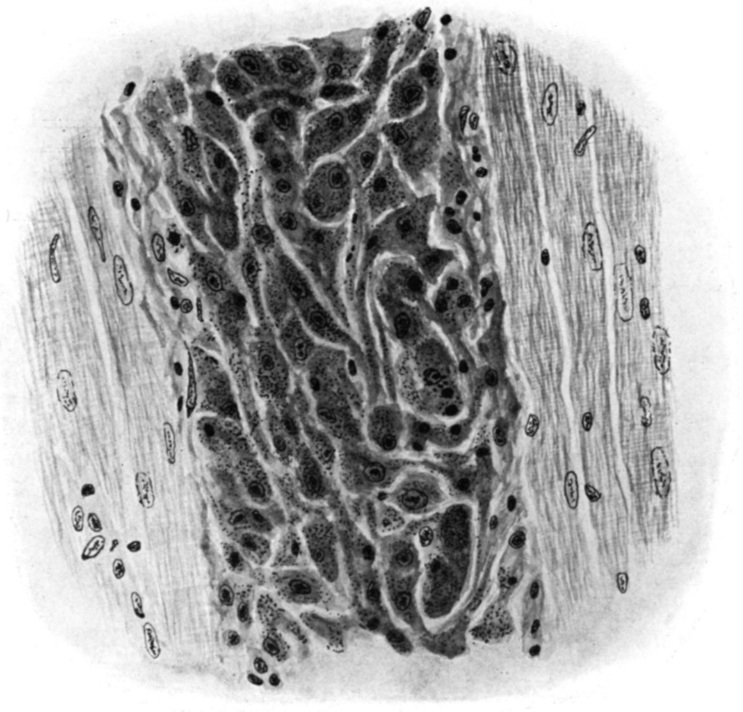

FIG. 2.—Part of a lesion consisting of large mononuclear cells closely crowded together and filled with organisms. From the heart of a rabbit dying 13 days after injection of streptococcus (236) from peritonitis secondary to sore throat.

Other lesions which cannot be so definitely connected with blood or lymph vessels consist of bacteria and disintegrating muscle fibers and cells with marked nuclear fragmentation in and around them. About these there is a very little necrosis of the muscle fibers, and polymorphonuclear leukocytes are quite abundant between the fibers.

*Changes in a rabbit dying spontaneously seven days after a single intravenous injection of a 24-hour growth of a streptococcus (218) isolated by Dr. Davis from the serofibrinous exudate of pleurisy following sore throat.*—There are but few lesions in these sections.

Two or three collections of from 15–25 cells are found in some sections, in others one somewhat larger lesion is found. The small collections contain chiefly large mononuclear cells rather lightly stained which have large, oval, unevenly stained nuclei. Many of these cells contain organisms. With these cells are smaller ones which have more deeply stained round nuclei. There is no necrosis about these regions. The largest lesion practically fills the field (Obj. 1/12, Oc. 1), and consists of a few remnants of necrotic muscle fibers, many large mononuclear cells with lightly stained granular cytoplasm, and a few smaller cells with more deeply stained nuclei, and a considerable number of new connective tissue cells.

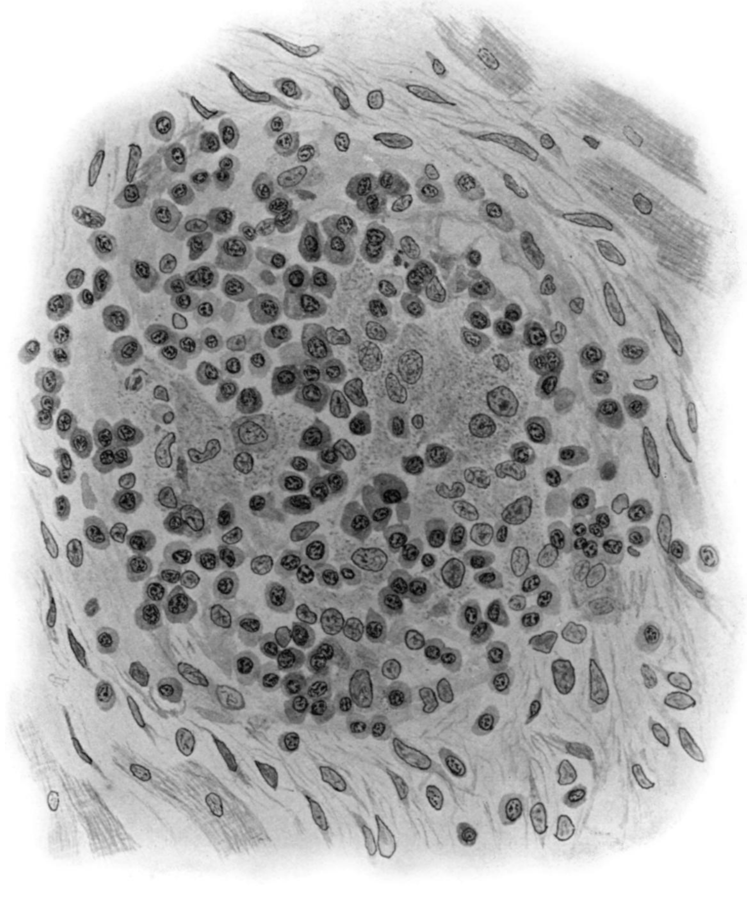

FIG. 3.—Mononuclear cells in a focal lesion from the heart of a rabbit dying two months after the first injection of streptococcus viridans (169).

*Changes in a rabbit killed 13 days after a single intravenous injection of a 24-hour growth of streptococcus (236) on a single blood agar slant.*—Three lesions are found in sections taken from two different places. The largest is about 1.5–0.5 mm. in diameter with its long axis in the direction of the muscle fibers. The other lesions are less than half as large and of the same character. They are composed of large mononuclear cells of variable size and indefinite outline closely crowded together. Nearly all these cells contain organisms so numerous in some cells that they cannot be counted with accuracy; in others they number from 10–50. There are no polymorphonuclear leukocytes within or about these lesions (Fig. 2).

*Changes in a rabbit dying during intracardial injection of a 24-hour growth on two blood agar slants of a streptococcus viridans (169) obtained by Dr. Davis from the heart valves of a man who long had suffered with endocarditis. The same streptococcus was found during life in the tonsils. Numerous tonsillar abscesses were present. This streptococcus produced endocarditis but not arthritis in rabbits. Three other intravenous injections had been made in this rabbit over a period of two months at intervals of 14, 21, and 14 days.*—The largest number of lesions contain degenerating muscle fibers which stain more deeply than the normal fibers and in some of the lesions they stain very intensely. Surrounding many of the fibers or grouped at one side are several nuclei which give them the appearance of giant cells. Large mononuclear cells are present in all these regions, sometimes arranged in groups but generally scattered in not very large numbers quite evenly throughout the lesion. Large multinucleated giant cells are also present in many of the lesions (Figs. 3 and 4). There is an increase in connective tissue in and about these regions. There is also a considerable number of lesions which contain no degenerating muscle fibers and are composed almost entirely

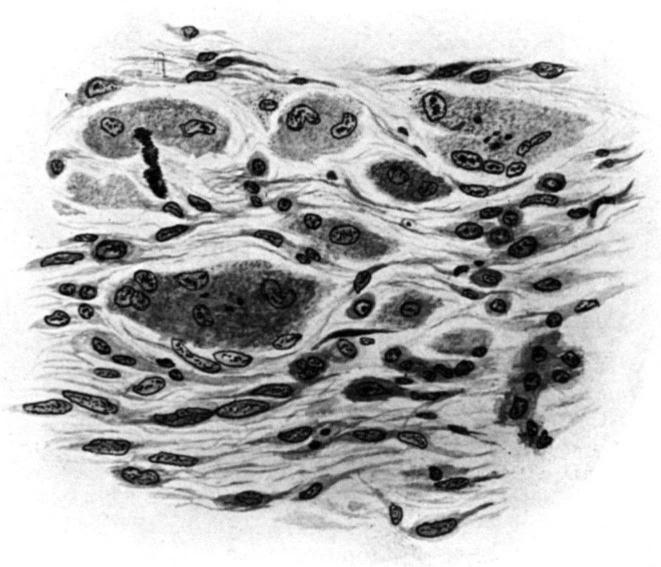

FIG. 4.—Nodule with multinucleated cells in the heart of a rabbit dying two months after the first injection of streptococcus viridans (169).

of mononuclears (Figs. 3 and 4). In some, the cells occupying the center of the lesion are very large with round or oval lightly stained nuclei and a large amount of granular cytoplasm in which bacteria are often seen. The bacteria are not numerous and in marked contrast with the great numbers found within similar cells in Rabbit 236 dying 13 days after inoculation. The outlines of these cells are not sharply defined. About the center are many smaller, more deeply stained cells, which are irregularly shaped and definitely outlined, and have round, rather deeply stained and eccentrically placed nuclei. The cytoplasm is fairly abundant, the width of the rim varying from a fourth to the entire diameter of the nucleus. In a few of these lesions are also a considerable number of polymorphonuclear leukocytes many of which are eosinophiles. A few of these lesions are not sharply marked off from the surrounding tissue, but there is a diffuse infiltration of cells among the muscle fibers. One lesion, which differs from the rest, consists of a vessel wall which is occupied by a pink-stained, homogeneous material surrounded by polymorphonuclear leukocytes, many of which are eosinophiles, together with a few large mononuclear cells. The vessel wall is infiltrated with leukocytes and mononuclear cells and a short distance away are small collections of cells which possess many of the features of plasma cells.

*Changes in a rabbit killed 24 hours after intravenous injection of the 24-hour growth on blood agar slants of the streptococcus viridans already referred to (169). Other injections had been given over a period of three months at intervals of 4, 8, 7, 2, 14, 16, and 12 days each. The first two were of the 24-hour growth on one blood agar slant of a streptococcus mucosus (28) isolated by Dr. Davis from the middle ear. Each of the remaining injections were of the 24-hour growth on five blood agar slants of the streptococcus viridans previously mentioned.*—Sections were made from three different places and lesions found in all. Some are small, not numerous, of the cellular type, containing 15 to 50 cells, generally mononuclears. Others, which are several times larger, are made up of polymorphonuclear leukocytes and mononuclear cells without necrosis. In some of the larger ones the polymorphonuclear leukocytes are more numerous, the center is occupied by leukocytes surrounded by a rather uniform mixture of leukocytes and mononuclear cells with a considerable number of eosinophiles scattered throughout. Both the smaller and the larger lesions are not sharply demarcated, and the muscle fibers appear quite unchanged.

In the relative absence of necrosis and of polymorphonuclear leukocytes no less than in the abundance of, and apparently large rôle played by, the large, so-called "endothelial" phagocytic leukocytes, the focal lesions produced in the heart muscles of these rabbits are peculiar. These characteristics are maintained throughout all the varying phases of their development, and they are the features which have been emphasized especially by Coombs but also by others, as distinctive of the focal lesions in the human heart in rheumatism. All of the streptococci, except the viridans (169), produced arthritis in rabbits. The differences in the changes are not marked when allowance is made for the varying periods at which the examinations were made. The oldest lesions, those in rabbits killed two and three months after injections of streptococcus viridans, were the only ones in which giant cells were found, which different writers have likened to the multinuclear cells in certain sarcomas and in the pseudoleukemic process. The alterations vary so little in their general nature as studied in the varying stages of their development that it seems reasonable to expect that other streptococci than the viridans may also produce focal changes with these peculiar giant cells.

Wächter[1] mentions having produced changes in the rabbit's heart resembling those or human rheumatism with a streptococcus viridans isolated from the heart's blood at the postmortem examination of a man aged 29, who died of an acute articular rheumatism. The chief result of subsequent experiments reported by Bracht and Wächter[2] was the production of changes in rabbits' hearts which were different from those caused by the ordinary streptococcus pyogenes (hemolyticus) but not identical with those in the human myocardium.[3] In the endeavor to produce myocarditis in rabbits, Bracht and Wächter used streptococci recovered from the blood of the heart chambers of two individuals dying from rheumatism. Of 10 rabbits seven were found to have a myocarditis. The authors describe the changes in three of them. One of their illustrations shows lesions quite similar to those I found were produced by the milk-epidemic streptococci as well as those caused by the viridans. Bracht and Wächter used 24-hour broth cultures and several intravenous injections of from 4 to 5 cm. The changes reported were observed in rabbits killed on the 9th, 10th, and 16th days. In five of the seven rabbits an endocarditis was present. In a number of the hearts I examined, endocardial lesions were also present. The examinations I have made of changes produced in the rabbit heart by an ordinary hemolyzing streptococcus pyogenes are too few to compare with those described in the foregoing protocols.

The experimental production in rabbits of these minute, disseminated regions of infection, their close morphological correspondence to the focal lesions in the human heart in acute articular rheumatism, and the fortunately exceptional characteristics of the changes, which make comparison so easy, obviously lead to the suspicion that they all have a similar etiology. As is well known, the ordinary streptococcus pyogenes produces in man, as well as in rabbits and other animals, minute abscesses with a marked infiltration of polymorphonuclear leukocytes, changes quite different from those forming the subject of this report. It may be well also to recall that involvement of the joints took place in many of the patients with epidemic sore throat, from whom the streptococci used to produce these lesions were obtained.

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[1] *München. med. Wchnschr.*, 1908, 55, p. 1101.

[2] *Deutsche Arch. f. klin. Med.*, 1909, 96, p. 493.

[3] L. Aschoff, *Pathologische Anatomie*, Jena, 2d ed., 2, p. 33.